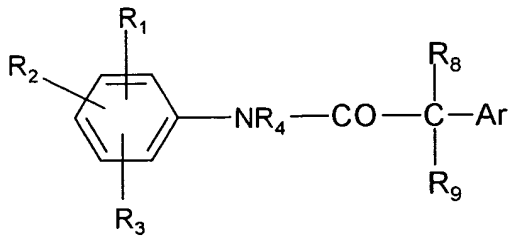
Patent Claims

1. Carboxylic acid amides of general formula



(I),

R_1 denotes a C_{3-7}-cycloalkyl-carbonyl group wherein

the methylene group in the 3 or 4 position in a C_{5-7}-cycloalkyl-carbonyl group may be replaced by an -NH group wherein

the hydrogen atom of the -NH group may be replaced by a C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl, phenylcarbonyl or phenylsulphonyl group,

a C_{1-6}-alkylcarbonyl group optionally terminally substituted in the alkyl moiety by an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a group of formula R_fR_gN-$(CH_2)_m$-$(R_h)N$-CO wherein
R_f, R_g and R_h independently of one another each denote a hydrogen atom or a C_{1-3}-alkyl group and
m denotes one of the numbers 2, 3, 4, 5 or 6,

a phenylcarbonyl, naphthylcarbonyl or heteroarylcarbonyl group,

a C_{1-3}-alkyl group monosubstituted by a hydroxy group or terminally disubstituted by a phenyl and a hydroxy group wherein

the phenyl substituent may be substituted by an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a 4- to 7-membered cycloalkyleneimino-carbonyl or cycloalkyleneimino-sulphonyl group substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a C_{3-7}-cycloalkylamino group which is substituted at the nitrogen atom by a C_{1-3}-alkyl-amino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

or, if R_5 denotes an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group and/or at least one of the groups R_8 or R_9 denotes a C_{1-3}-alkyl group, an unsubstituted 4- to 7-membered cycloalkyleneimino-carbonyl or cycloalkyleneimino-sulphonyl group, a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkylamino group,

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy or C_{1-3}-alkoxy group,

R_3 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_4 denotes a hydrogen atom or a C_{1-3}-alkyl group optionally substituted by a carboxy group or a group which may be converted into a carboxy group in vivo,

Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while

R_5 denotes a cyano group, an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

R_6 denotes a hydrogen, fluorine, chlorine or bromine atom, a trifluoromethyl, C_{1-3}-alkyl, hydroxy, hydroxy-C_{1-3}-alkyl, C_{1-3}-alkoxy, C_{1-3}-alkoxy-C_{1-3}-alkyl, carboxy, carboxy-C_{1-3}-alkyl, carboxy-C_{1-3}-alkoxy, C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy, phenyl-C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)amino group and

R_7 denotes a hydrogen, fluorine, chlorine or bromine atom or a C_{1-3}-alkyl group,

or a thienylene, thiazolylene, pyridinylene, pyrimidinylene, pyrazinylene or pyridazinylene group optionally substituted in the carbon skeleton by a C_{1-3}-alkyl group,

R_8 and R_9, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group,

while the term heteroaryl group mentioned above denotes a 5-membered heteroaryl group bound via a carbon or nitrogen atom which contains

an imino group optionally substituted by a C_{1-3}-alkyl group, an oxygen or sulphur atom,

an imino group optionally substituted by a C_{1-3}-alkyl group or an oxygen, sulphur or nitrogen atom,

an imino group optionally substituted by a C_{1-3}-alkyl group and two nitrogen atoms or

an oxygen or sulphur atom and two nitrogen atoms,

or a 6-membered heteroaryl group which contains one or two nitrogen atoms,

while a phenyl ring may be fused to the abovementioned 5- or 6-membered heteroaryl groups via two adjacent carbon atoms and the bicyclic heteroaryl groups thus formed may be bound via the heteroaromatic or carbocyclic moiety,

and the unsubstituted or monosubstituted phenyl and naphthyl groups mentioned in the definition of the abovementioned groups, or the unsubstituted or monosubstituted phenyl and naphthyl groups contained in these groups, as well as the abovementioned heteroaryl groups may additionally be substituted at a carbon atom in each case by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, unless otherwise stated,

the carboxy groups mentioned in the definition of the abovementioned groups may be replaced by a group which may be converted *in vivo* into a carboxy group or by a group which is negatively charged under physiological conditions, and

the amino and imino groups mentioned in the definition of the abovementioned groups may be substituted by a group which can be cleaved *in vivo*,

and the compound

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

the stereoisomers and the salts thereof.

2. Carboxylic acid amides of general formula I according to claim 1, wherein

R_1 denotes a C_{5-7}-cycloalkyl-carbonyl group wherein the methylene group in the 3 or 4 position is replaced by an -NH group wherein

the hydrogen atom may be replaced by a C_{1-3}-alkyl, C_{1-3}-alkyl-carbonyl or phenylcarbonyl group,

a C_{1-3}-alkyl-carbonyl group optionally terminally substituted in the alkyl moiety by a C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a group of formula $R_fR_gN-(CH_2)_m-(R_h)N-CO$, wherein

R_f, R_g and R_h independently of one another each denote a hydrogen atom or a C_{1-3}-alkyl group and

m denotes one of the numbers 2, 3 or 4,

a phenylcarbonyl or heteroarylcarbonyl group,

while the heteroaryl moiety contains a 6-membered heteroaryl group which contains one or two nitrogen atoms and to which a phenyl ring may be fused via two adjacent carbon atoms, while the bicyclic heteroaryl groups thus formed may be bound via the heteroaromatic or carbocyclic moiety, e.g. a 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, quinoxalinyl or quinazolinyl group,

a C_{1-3}-alkyl group monosubstituted by a hydroxy group or terminally disubstituted by a phenyl group and a hydroxy group wherein

the phenyl substituent may be substituted by an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group,

a 4- to 7-membered cycloalkyleneimino-carbonyl group substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, C_{1-4}-alkoxy-carbonyl-amino-C_{1-3}-alkyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

a C_{5-7}-cycloalkylamino group which is substituted at the nitrogen atom by a C_{1-3}-alkyl-amino-C_{1-3}-alkyl or di-(C_{1-3}-alkyl)amino-C_{1-3}-alkyl group,

or, if R_5 denotes an amino-C_{1-3}-alkyl or C_{1-3}-alkylamino-C_{1-3}-alkyl group and/or at least one of the groups R_8 or R_9 denotes a C_{1-3}-alkyl group, an unsubstituted 4- to

7-membered cycloalkyleneiminocarbonyl group, a C_{5-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{5-7}-cycloalkylamino group,

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl, trifluoromethyl or C_{1-3}-alkoxy group,

R_3 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R_4 denotes a hydrogen atom or a C_{1-3}-alkyl group,

Ar denotes a phenyl group substituted by the groups R_5 and R_6 wherein

R_5 denotes a cyano group, an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, an amino-C_{1-3}-alkyl or C_{1-3}-alkylamino-C_{1-3}-alkyl group and

R_6 denotes a hydrogen, fluorine, chlorine or bromine atom, a trifluoromethyl, C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy group, and

R_8 and R_9, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group,

while the unsubstituted or monosubstituted phenyl groups mentioned in the definition of the abovementioned groups, or the unsubstituted or monosubstituted phenyl moieties contained in these groups, as well as the abovementioned heteroaryl groups may additionally be substituted at a carbon atom in each case by a fluorine, chlorine or bromine atom, by a trifluoromethyl, C_{1-3}-alkyl or C_{1-3}-alkoxy group, unless otherwise stated,

and the compound

2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

the isomers and the salts thereof.

3. Carboxylic acid amides of general formula I according to one of claims 1 or 2, wherein

the groups R_1 to R_4, R_8 and R_9 are defined as in claim 1 or 2, but R_1 in the 4 position is bound to the phenyl group contained in formula I and

Ar denotes a phenyl group disubstituted by the groups R_5 and R_6, while

R_5 is bound in the 3 position if R_6 denotes a hydrogen atom, or is bound in the 5 position if R_6 assumes a meaning other than the hydrogen atom, and an amidino group optionally substituted by one or two C_{1-3}-alkyl groups, an amino-C_{1-3}-alkyl or C_{1-3}-alkylamino-C_{1-3}-alkyl group and

R_6 denotes a hydrogen atom or a trifluoromethyl, C_{1-3}-alkyl, hydroxy, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy group bound in the 2 position,

the isomers and the salts thereof.

4. Carboxylic acid amides of general formula I according to claim 1, wherein

R_1 is bound in the 4 position of the phenyl group of formula I and denotes

a C_{5-7}-cycloalkyl-carbonyl group wherein the methylene group in the 3 or 4 position is replaced by an -NH group,

a phenylcarbonyl group optionally substituted by a fluorine, chlorine or bromine atom or by a C_{1-3}-alkyl group,

a C_{1-3}-alkyl group terminally disubstituted by a phenyl and a hydroxy group wherein

the phenyl substituent may be monosubstituted by a C_{1-3}-alkyl or an amidino group or may be disubstituted by a C_{1-3}-alkyl and an amidino group,

a 5- to 7-membered cycloalkyleneimino-carbonyl group substituted by an amino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl, C_{1-4}-alkoxy-carbonyl-amino-C_{1-3}-alkyl, aminocarbonyl or C_{1-3}-alkylamino-carbonyl group,

or, if R_5 denotes an amino-C_{1-3}-alkyl group and/or at least one of the groups R_8 or R_9 denotes a C_{1-3}-alkyl group, an unsubstituted 5- to 7-membered cycloalkyleneimino-carbonyl group and

R_2 denotes a hydrogen atom or a substitutent bound in the 3 position of the phenyl group, selected from among fluorine, chlorine, bromine, C_{1-3}-alkyl and trifluoromethyl,

R_3 and R_4 each denote a hydrogen atom,

Ar denotes a phenyl group substituted by the groups R_5 and R_6 wherein

R_5 is bound in the 3 position if R_6 denotes a hydrogen atom, or is bound in the 5 position if R_6 assumes a meaning other than the hydrogen atom, and an amidino or amino-C_{1-3}-alkyl group and

R_6 denotes a hydrogen atom or a hydroxy, C_{1-3}-alkoxy, carboxy-C_{1-3}-alkoxy or C_{1-4}-alkoxy-carbonyl-C_{1-3}-alkoxy group bound in the 2 position, and

R_8 and R_9, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group,

the isomers and the salts thereof.

5. The following compounds of general formula I according to claim 1:

(1) (L)-2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-aminocarbonyl-pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(2) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(2-tert.butoxycarbonylaminomethyl-piperidin-1-yl-carbonyl)-phenyl]-acetamide,

(3) 2-(5-aminomethyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(4) 2-(3-carbamimidoyl-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-2,2-dimethylacetamide,

(5) 2-(5-carbamimidoyl-2-ethoxycarbonylmethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(6) 2-(5-carbamimidoyl-2-carboxymethyloxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

(7) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(piperidin-3-yl-carbonyl)-phenyl]-acetamide,

(8) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-(3-methyl-4-benzoyl-phenyl)-acetamide,

(9) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(hydroxy-phenyl-methyl)-phenyl]-acetamide,

(10) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-{4-[(3-carbamimidoyl-phenyl)-hydroxy-methyl]-3-methyl-phenyl}-acetamide,

(11) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-methyl-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-2,2-dimethylacetamide and

(12) 2-(5-carbamimidoyl-2-hydroxy-phenyl)-N-[3-chloro-4-(pyrrolidin-1-yl-carbonyl)-phenyl]-acetamide,

wherein the amidino group may additionally be substituted by a C_{1-6}-alkoxycarbonyl or phenylcarbonyl, and the salts thereof.

6. Physiologically acceptable salts of the compounds according to claims 1 to 5 with the exception of those compounds wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, and R_5 denotes a cyano group.

7. Pharmaceutical compositions containing a compound according to at least one of claims 1 to 5 with the exception of those compounds wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7 and R_5 denotes a cyano group, or a salt according to claim 6 optionally together with one or more inert carriers and/or diluents.

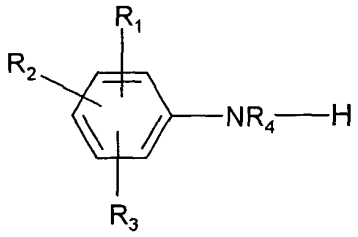
8. Use of a compound according to at least one of claims 1 to 5 with the exception of those compounds wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7 and R_5 denotes a cyano group, or a salt according to claim 6 for preparing a pharmaceutical composition with an antithrombotic activity.

9. Process for preparing a pharmaceutical composition according to claim 7, characterised in that a compound according to at least one of claims 1 to 5 with the exception of those compounds wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7 and R_5 denotes a cyano group, or a salt according to claim 6 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

10. Process for preparing the compounds according to claims 1 to 6, characterised in that

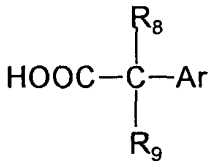
a) in order to prepare a compound of general formula I wherein
Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_6 and R_7 are defined as in claims 1 to 5 and R_5 denotes an amidino group,

a compound of general formula



(II),

wherein R_1 to R_4 are defined as in claims 1 to 5, is acylated with a carboxylic acid of general formula

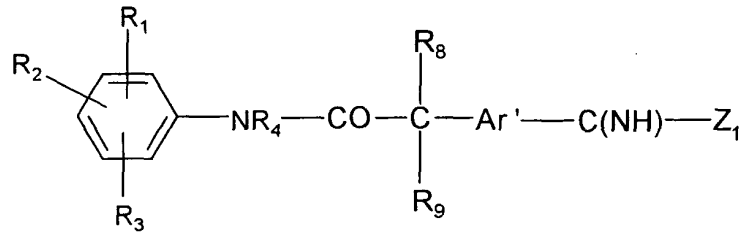


(III),

wherein R_8 and R_9 are defined as in claims 1 to 5 and Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_5 denotes a cyano group and R_6 and R_7 are defined as in claims 1 to 5, or with the reactive derivatives thereof, and the resulting cyano compound is then converted into an amidino compound, or

b) in order to prepare a compound of general formula I wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_6 and R_7 are defined as in claims 1 to 5 and R_5 denotes an amidino group optionally substituted by one or two C_{1-3}-alkyl groups,

a compound of general formula



(IV),

optionally formed in the reaction mixture

wherein

R_1 to R_4, R_8 and R_9 are defined as in claims 1 to 5, Ar' denotes a phenyl or naphthyl group substituted by the groups R_6 and R_7, while R_6 and R_7 are defined as in claims 1 to 5, and

Z_1 denotes an alkoxy, aralkoxy, alkylthio or aralkylthio group, is reacted with an amine of general formula

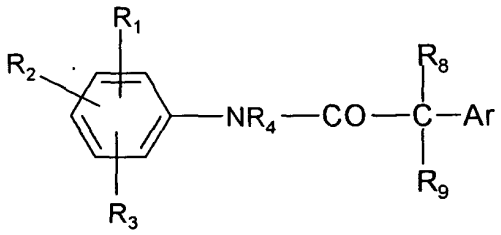
$$H - R_{10}NR_{11} \text{ , (V)}$$

wherein

R_{10} and R_{11}, which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group, or with the salts thereof, or

c) in order to prepare a compound of general formula I wherein Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7, while R_6 and R_7 are defined as in claims 1 to 5 and R_5 denotes an aminomethyl, C_{1-3}-alkylaminomethyl or di-(C_{1-3}-alkyl)aminomethyl group,

a compound of general formula



(I'),

wherein

Ar denotes a phenyl or naphthyl group substituted by the groups R_5, R_6 and R_7,

R_1 to R_4 and R_6 to R_9 are defined as in claims 1 to 5 and

R_5 denotes a cyano group,

is catalytically hydrogenated and optionally then alkylated with a compound of formula

$$R_{12} - Z_2 \qquad \text{(VI)},$$

wherein R_{12} denotes a C_{1-3}-alkyl group and Z_2 denotes a leaving group, and

subsequently, if desired, a compound of general formula I thus obtained which contains an amino or imino group is converted by means of a corresponding acyl derivative into a corresponding acyl compound of general formula I and/or

a compound of general formula I thus obtained which contains an esterified carboxy group is converted by hydrolysis into a corresponding carboxylic acid of general formula I and/or

a compound of general formula I thus obtained which contains a carboxy group is converted by esterification into a corresponding ester and/or

any protecting group used in order to protect reactive groups during the reactions is cleaved and/or

a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly, for pharmaceutical use, into the physiologically acceptable salts thereof with an inorganic or organic acid or base.